PROCESS FOR PREPARING IMIDAZO/4,5-C/QUINOLINES

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Abstract of **HU 34479 (A2)**

Imidazo-(4,5c)-quinoline derivs. of formula (I) and their pharmaceutically acceptable salts are useful as tranquillisers and/or anti-depressants, cramp-preventers, pain-killers, anti-peristaltic or secretion inhibitors. - In the formula R1 is H, straight or branched 1-4C alkyl opt. substd. with hydroxyl or alkoxy lgps., phenyl substd. with alkoxyl, aralkyl opt. substd. with one or more halogens or alkoxy gps., dialkyl-amino-alkyl, amino or -NH-CO-R, where R is H, straight or branched 1-10C alkyl, aralkyl or aryl. R1 may be -N=R3R4, where R3 and R4 are independently H, 1-4C alkyl or aryl. R2 is H, straight or branched 1-4C alkyl phenyl or aralkyl opt. substd. with halogen, alkoxy, thio, alkyl-thio, alkyl-sulphinyl or alkyl-sulphonyl. R7 and R8 are H or alkoxy.

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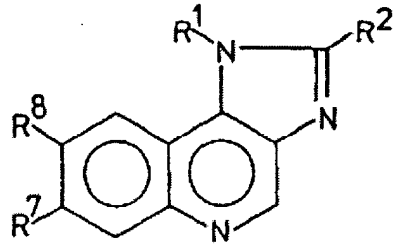
(54) Method for preparation of imidazo(4,5-c)quinolines

(57) Abstract

The subject of the invention is a method for preparation of the new imidazo(4,5-c)quinolines of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group possibly substituted with a hydroxyl group, or a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group or a phenyl-(1-4 carbon atom) alkyl group possibly substituted by a 1-4 carbon atom alkoxy group or one or more halogen atom in the benzene ring or a di(1-4 carbon atom) alkylamino-(1-4 carbon atom) alkyl group, amino group, -NH-CO-R group (where the meaning of R is a 1-10 carbon atom straight or branched chain alkyl group, a phenyl-1-4 carbon atom alkyl group or a phenyl group), the meaning of R2 is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group, a 1-4 carbon atom straight or branched chain alkyl group, or a phenyl group possibly substituted with a 1-4 carbon atom alkoxy group, or a phenyl-1-4 carbon atom-alkyl group, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon atom alkoxy group, and their pharmacologically applicable salts.

The compounds of the invention primarily have a tranquilizing and/or antidepressant, antispasmodic, analgesic, antiperistaltic, and antisecretory action.



The subject of the invention is a method for preparation of the new imidazo(4,5-c)quinolines of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group possibly substituted with a hydroxyl group, or a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group or a phenyl-(1-4 carbon atom) alkyl group possibly substituted by a 1-4 carbon atom alkoxy group or one or more halogen atom in the benzene ring or a di(1-4 carbon atom) alkylamino-(1-4 carbon atom) alkyl group, amino group, -NH-CO-R group (where the meaning of R is a 1-10 carbon atom straight or branched chain alkyl group, a phenyl-1-4 carbon atom alkyl group or a phenyl group), the meaning of R2 is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group, or a phenyl group possibly substituted with a 1-4 carbon atom alkoxy group, or a phenyl-1-4 carbon atom-alkyl group, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon atom alkoxy group, and their pharmacologically acceptable salts, in such a way that

a) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group possibly substituted with a 1-4 carbon atom alkoxy group, a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group, a phenyl-(1-4 carbon atom) alkyl group possibly substituted by a 1-4 carbon atom alkoxy group or one or more halogen atom in the benzene ring or a di(1-4 carbon atom) alkylamino-(1-4 carbon atom) alkyl group, the meaning of R2 is as given, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon atom alkoxy group, we react any compound of general formula (II), where R1, R7 and R8 in the formula have the above meaning, with an orthoester of general formula (III), where the meaning of R2 in the formula is as given above, the meaning of Alk is a 1-4 carbon alkyl group, or with a carboxylic acid of general formula (IV), where the meaning of R2 in the formula is as given above, or with an aldehyde of general formula (V), where the meaning of R2 in the formula is as given above, or

b) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon straight or branched chain alkyl group possibly substituted with a 1-4 carbon alkoxy group, a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group, a phenyl-(1-4 carbon) alkyl group possibly substituted by a 1-4 carbon alkoxy group or one or more halogen atoms in the benzene ring or a di(1-4 carbon) alkylamino-(1-4 carbon) alkyl group, the meaning of R2 is as given, but other than hydrogen atom, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon alkoxy group, we react any compound of general formula (II), where R1, R7 and R8 in the formula have the above meaning, with an anhydride of general formula (IX), where the meaning of R2 in the formula is as given above, or

c) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1, R2, R7 and R8 in the formula is as above, we acylate any compound of general formula (VIII), where the meaning of R1, R7 and R8 in the formula is as above, with an anhydride of general formula (IX), where the meaning of R2 in the formula is as given above, or with an acid halide of general formula (X), where the meaning of R2 in the formula is as given above and the meaning of X is a halogen atom, we reduce the resulting compound of general formula (VI), where the meaning of R1, R2, R7 and R8 in the formula is as above, and we treat the resulting

compound of general formula (VII), where the meaning of R1, R2, R7 and R8 in the formula is as above, with an acid catalyst in a polar solvent, preferably alcohol, dimethyl formamide, or dimethyl sulfoxide, or a mixture of these, at temperature of 0 to 200 degrees C, or

d) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, amino group, -NH-CO-R group (where the meaning of R is a 1-10 carbon straight or branched chain alkyl group, a phenyl-1-4 carbon alkyl group or a phenyl group), the meaning of R2, R7 and R8 is as above, we treat any compound of general formula (XI), where the meaning of R and R2 in the formula is as above, with acid and if desired we boil the obtained compound of general formula (Ia), where the meaning of R and R2 in the formula is as above, with concentrated acid, and if so desired we react the obtained compound of general formula (Ib), where the meaning of R2 in the formula is as given above, with acidic sodium nitrite, or

e) for the preparation of compounds of general formula (Ia), belonging to the group of compounds with general formula (I), where the meaning of R in the formula is as given above, we acylate any compound of general formula (Ib), where the meaning of R2 in the formula is as given above, with a compound containing a group of general formula R-CO-, where the meaning of R in the formula is as given above, and if so desired we transform the resulting compounds of general formula (I) into pharmaceutically acceptable acid addition salts, or liberate the base from the salt.

Only a few representatives of the imidazo(4,5-c)quinolines are known in the technical literature, thus, the article in J. Med. Chem. 11 (1) 87-92 (1968) reports on the preparation of 1-(2-piperidyl-ethyl)-imidazo(4,5-c)quinoline hydrochloride, without giving physical constants or biological data.

Soviet patent specification No. 509 588 describes the synthesis of 2-oxo-3-phenyl-1H-imidazo(4,5-c)quinoline-6-carboxylic acid – again, without any biological data.

We prepare those compounds of general formula (I), where the meaning of R1 is a hydrogen atom, or an alkyl, phenyl, aralkyl, dialkyl-amino-alkyl group, the meaning of R2, R7, R8 is as above, by reacting a compound of general formula (II), where the meaning of R1, R7, R8 is as above, with orthoesters of general formula (III), where the meaning of R2 in the formula is as above, and Alk designates a 1-4 carbon alkyl group. We carry out the reaction preferably in excess of orthoester, at such a temperature as falls between the boiling point of the orthoester used and the alcohol being formed. A condition for completion of the reaction is the continual removal of the alcohol being formed from the system.

The article JACS 61 3322 (1939) and J. Chem. Soc. 1950, 392, describes the preparation of compounds of general formula (II).

According to another advantageous method for preparation of the above compounds of general formula (I), we react a compound of general formula (II), where the meaning of R1, R7, R8 is as above, with an acid of general formula (IV), where the meaning of R2 is as above. We carry out the reaction preferably with the use of equivalent acid, in presence of a phosphorus halide (POCl3, POBr3, PCl5, etc.), in inert solvent (especially in aromatic hydrocarbons), or in excess phosphorus halide, at temperature between 20 and 140 degrees C, preferably at the boiling point of the mixture.

We can also carry out the same method by boiling compounds of general formula (II) with excess acid of general formula (IV).

According to another advantageous method for preparation of the above compounds belonging to the group of compounds of general formula (I), we react any compound of general formula (II), where the meaning of R1, R7, R8 is as above, with an aldehyde of general formula (V), where the meaning of R2 is as above. We carry out the reaction such that we react a compound of general formula (II), or its salt, with an equimolar quantity of aldehyde of general formula (V), or its adduct formed with sodium hydrogen sulfite, in a solvent, especially alcohols. We transform the resulting Schiff base at elevated temperature into the imidazo(4,5-c)quinoline. We perform the ring closure preferably in nitrobenzene at temperature between 150 and 210 degrees C.

Another possibility for preparation of the compounds of general formula (I) described in the foregoing is cyclization of any compound of general formula (VII), where the meaning of R1, R2, R7, R8 is as above. We carry out the cyclization in polar solvent, such as alcohol, dimethyl formamide, dimethyl sulfoxide, or a mixture of these, in the presence of an acid catalyst, at temperature between 0 and 200 degrees C.

The compounds of general formula (VII), which are likewise new, can be prepared in that we reduce a compound of general formula (VI), where the meaning of R1, R2, R7 and R8 is as above. For example, the reduction can be carried out in the presence of palladium charcoal catalyst, with hydrogen gas, but other reduction methods can also be used.

The compounds of general formula (VI), which are likewise new, can be prepared in that we acylate a compound of general formula (VIII), where the meaning of R1, R7, R8 is as above, with a carboxylic anhydride of general formula (IX), where the meaning of R2 is as above, but cannot be hydrogen, or with an acid halide of general formula (X), where the meaning of R2 is as above and X = halogen atom, preferably the chlorine or bromine atom.

The compounds of general formula (VIII) are known from the paper J. Am. Chem. Soc. 69 365-71 (1947), or can be prepared by the method described there.

Another possibility for preparation of the compounds of general formula (I) discussed in the foregoing is to react a compound of general formula (II), where the meaning of R1, R7, R8 is as above, with an acid anhydride of general formula (IX), where the meaning of R2 is as above. We carry out the reaction in inert solvent (benzene, toluene, xylene) or in excess of the anhydride, at temperature between 50 and 180 degrees C.

We can prepare the compounds of general formula (Ia), belonging to the group of compounds of general formula (I), in which the meaning of R1 is a R-CO-NH group, while the meaning of R2 is as above, by subjecting compounds of general formula (XI), in which the meaning of R and R2 is as above, to ring rearrangement.

We can prepare the compounds of general formula (Ib), belonging to the group of compounds of general formula (I), in which the meaning of R1 is a NH2 group, while the meaning of R2 is as above, by deacylating compounds of general formula (Ia), where the meaning of R and R2 is as above.

We can prepare the compounds of general formula (Id), belonging to the group of compounds of general formula (I), in which the meaning of R1 is a hydrogen atom, while the meaning of R2 is as above, by deaminating compounds of general formula (Ib).

We can advantageously prepare the compounds of general formula (Ia) by treating a compound of general formula (XI), whose preparation is described by the published European patent application No. 38 528, in polar solvent, in the presence of a mineral acid, at temperature between 50 and 100 degrees C. As the solvent, one will consider water, alcohols (methanol, ethanol, propanol, butanol, etc.), dimethyl sulfoxide, dimethyl formamide, or a mixture of these; as the mineral acid, one can use hydrochloric acid, sulfuric acid, phosphoric acid, etc. The ring rearrangement occurring under the action of the acid is also easily observable with the naked eye: the colored compound of general formula (XI), containing a six-member ring, loses color along with its transformation into a five-member ring.

We prepare the compounds of general formula (Ib) by boiling compounds of general formula (Ia) with concentrated hydrochloric acid.

We prepare the compounds of general formula (Ic) by reacting amino compounds of general formula (Ib) with oxocompounds of general formula R3R4CO in polar solvents (water, alcohols such as methanol, ethanol, propanol, butanol, etc., organic acids such as formic acid, acetic acid, etc.) or a mixture of these, or in excess of the oxocompound, at temperature between 20 and 140 degrees C, preferably at the boiling point of the mixture.

We prepare the compounds of general formula (Id) by treating amino compounds of general formula (Ib) with sodium nitrite in a mixture of water and mineral acid, preferably hydrochloric acid, at a temperature between –20 and +30 degrees C, preferably between 0 and 5 degrees C.

The compounds according to the invention possess significant tranquilizing and/or antidepressant, antispasmodic, analgesic, antiperistaltic, and antisecretory action.

We prove the action of the compounds according to the invention with the following pharmacological investigations and data.

Investigation methods

Acute toxicity in the mouse

We performed our investigations with white mice weighing 18-22 g, of both sexes, originating from the CFLP stock breeding facility. After the per os treatment, the animals were kept under observation for 7 days. Half of the dosage groups were male and half female animals. The animals were kept in a plastic box measuring 39 x 12 x 12 cm, with litter of wood shavings, in premises at room temperature. They received standard mouse food and tap water ad libitum. We determined the toxicity data with the Litchfield-Wilcoxon method. We dispensed the studied substance from suspension prepared with the help of TWEEN-80.

Spontaneous motility in the mouse

We performed our experiments according to Borsy et al, in groups consisting of 3-3 mice. One hour after the per os preparative treatment, we placed the animals in a 10-channel Dews type apparatus. We registered the number of light interruptions for 30 minutes.

Hexobarbital sleep in the mouse

We performed our studies with groups consisting of 6-6 mice. One hour after the per os treatment, we brought about sleep in both the control group and the group treated with the compound by administering 40 mg/kg i.v. hexobarbital.

Tetrabenazin ptosis antagonism in the mouse

We treated per os the groups consisting of 10-10 mice with the corresponding doses of compounds, and the control group with 0.5 vol. % of TW. After 30 minutes, we administered 50 mg/kg of Tetrabenazin i.p., and after 30, 60, 90 and 120 minutes we counted the animals with closed eyelids in each group.

Yohimbin toxicity potentiation in the mouse

We performed our studies by the Quinton method. We treated the groups consisting of 10-10 mice with 0.5 vol.% of TW, or the corresponding doses of the compound. One hour later we administered the sublethal dose of Yohimbin to the individual groups in a 20 mg/kg volume by i.p. route. One and 24 hours after this, we counted the deceased animals.

Investigation of pentetrazole spasm inhibition in the mouse

We performed our studies on white mice. We recorded the clonic and hind limb tonic extensor spasms occurring under the influence of an i.p. dose of pentetrazole of 125 mg/kg, as well as the mortality, in groups consisting of 6 animals. We administered the corresponding dose of the compound or the control substance one hour prior to giving the pentetrazole.

Inhibition of electroshock in the mouse

We performed our studies on the 20-25 g white mouse by the method of Swinyard et al. We produced an electric shock of 50 Hz, 45 mA, 0.4 seconds, using corneal electrodes. We used total inhibition of the hind limb extensor tonic spasm as the criterion for the anticonvulsive effect. We administered the substance being investigated or the base substance of the control one hour prior to the electroshock.

Acetic acid "writhing" test in the mouse

We gave 0.4 ml of 0.5% acetic acid intraperitoneally to mice weighing 20-25 g by the Newbould method. Between 5 and 10 minutes after giving the acetic acid, we counted the characteristic "writhing" reactions for all the animals and expressed the total "writhing" count after five minutes as a percentage of the values found for the control animals. We administered the substances being studied or the vehicle to the animals per os, one hour prior to giving the acetic acid. We investigated each dose in 12 animals.

Investigation of the effect on the gastrointestinal passage

We investigated the antiperistaltic action of the compound in white mice weighing 20-25 g with the method of Stickney et al. We administered the various doses of the compounds orally, 60 minutes before applying the 10% charcoal suspension. We treated the control group animals with the vehicle substance in the same way and time. We killed the mice 20 minutes after giving the charcoal suspension and measured the total length of small intestine and the length filled with charcoal. We calculated or evaluated the percentage inhibition as a ratio of the control.

Influencing of gastric secretion in the rat

We performed our investigations by the Shay surgical method. We used fasting rats of Wistar breed, weighing 200-250 g. During the 48-hour period of fasting, the animals were able to consume water ad libitum. We used groups consisting of 4 male and 4 female animals. On the day of the experiment, we applied a ligature to the pylorus of the animals under ether narcosis. We administered the doses of the compound being studied per os, 3 hours prior to the operation. We treated the same number of control group animals with tap water in the identical time and manner and volume. Four hours after the operation, we killed the animals with ether, took out the stomach after tying the cardia, took up the stomach contents, and measured the volume of gastric juices after centrifugation. Then, by titrating with 0.1 N NaOH, we determined the content of free acid, or total acidity. We converted the results to 100 g body weight per individual and then calculated the group average.

According to the invention, the following compounds have the most valuable pharmacological properties:

1-(hexanoyl-amino)-2-methyl-1H-imidazo-(4,5-c)quinoline.HCl

(1)

1-amino-2-methyl-1H-imidazo-(4,5-c)quinoline.HCl

(2)

1-amino-1H-imidazo-(4,5-c)quinoline.HCl

(3)

1H-imidazo-(4,5-c)quinoline.HCl

(4)

2-methyl-1H-imidazo-(4,5-c)quinoline.HCl

(5)

2-ethyl-1H-imidazo-(4,5-c)quinoline.HCl

(6)

1-methyl-1H-imidazo-(4,5-c)quinoline

(7)

2-phenyl-1H-imidazo-(4,5-c)quinoline.HCl

(8)

1-ethyl-1H-imidazo-(4,5-c)quinoline.HCl

(9)

1-(2-diethylamino-ethyl)-1H-imidazo-(4,5-c)quinoline.HCl
(10)
1-isopropyl-1H-imidazo-(4,5-c)quinoline.HCl
(11)
1-(3-dimethylamino-propyl)-1H-imidazo-(4,5-c)quinoline.HCl
(12)
2-(2-methoxy-phenyl)-1H-imidazo-(4,5-c)quinoline.ethane sulfonate
(13)
1-ethyl-2-ethyl-1H-imidazo-(4,5-c)quinoline.HCl
(14)

Results:

Compound:	LD50, mg/kg	Motility inhibition		Hexobarbital narc. pot.	
		ED50, mg/kg	TI	ED50, mg/kg	TI
1.	2000	140	14.3	170	11.8
2.	1500	170	8.8	170	8.8
3.	700	70	10.0	76	9.2
4.	900	100	9.0	180	5.0
8.	1000	170	5.9	75	13.3
9.	640	66	9.7	approx.130	4.9
10.	540	76	7.0	20	27.0
11.	600	80	8.3	17	35.0
12.	1800	250	7.2	approx.360	5.0
14.	700	74	9.5	36	19.0
Meprobamate	1100	270	4.1	260	4.2

Compound	LD50, mg/kg	Tetrabenazin ptosis ant.		Yohimbin tox. pot.	
		ED50, mg/kg	TI	ED50, mg/kg	TI
5.	1200	18	66.7	50	24
9.	approx.640	130	5	35	18
Amitryptilin	225	12	18.7	12.5	18

Compound	LD50, mg/kg	Pentetrazole spasm inhibition		MDS inhibition	
		ED50, mg/kg	TI	ED50, mg/kg	TI
8.	1000	66	15.2	115	8.7
13.	2000	140	14.2	200	10.0

Compound	LD50, mg/kg	Pentetrazole spasm inhibition	MDS inhibition

		ED50, mg/kg	TI	ED50, mg/kg	TI
14.	700	78	8.9	approx.140	5.0
Trimethadione	2050	490	4.3	400	5.3

Compound	LD50, mg/kg	Analgesic action, "writhing"	
		ED50, mg/kg	TI
1.	2000	110	18.2
2.	1500	115	13.1
3.	700	62.5	11.2
4.	900	135	6.7
9.	640	130	4.9
14.	700	80	8.7
Paracetamol	540	180	2.8
Acetyl salicylic acid	1500	240	6.25

Compound	LD50, mg/kg	Peristaltics inhibition	
		ED50, mg/kg	TI
3.	700	32	22
4.	900	0.8	1125
7.	420	30.0	14
6.	1000	200	5
9.	640	70	9
12.	1800	100	18
14.	700	40	17.5
Papaverine	380	185	2.1

Compound	LD50, mg/kg	Free HCl inhibition 50% inhibiting dose
1.	2000	150
2.	1500	175
3.	700	140 (-39%)x
4.	900	120 (-35%)x
5.	1200	50(-65%)x
Trithiozin	2000	250(-16%)x

x = ulcer inhibition observed at the screen dose

Furthermore, the subject of the invention is a method for preparation of a pharmaceutical product containing any of the compounds of general formula (I), in that we mix any compound of general formula (I) with the customary bases used in pharmaceutical technology and transform them into a pharmaceutical product, more precisely, a tablet, injection, solution, capsule.
We shall demonstrate our invention by the following examples, without our claim being limited to these:

Example 1

Preparation of 1H-imidazo(4,5-c)quinoline.HCl

We heat 23.2 g (0.1 mole) of 3,4-diamino-quinoline hydrochloride with 300 ml of triethyl orthoformate at 120-140 degrees C, while continually distilling off the ethanol formed from the reaction. When the removal of the ethanol is finished, we cool down the reaction mixture, adjust the reaction of the mixture to pH = 1 with ethanol hydrochloride, and dry the precipitated crystals. Weight: 18.5 g. Yield: 90%. Melting point: 316-318 degrees C (methanol), base m.p.: 282-284 degrees C.
In similar fashion, the following compounds can be prepared:

	Yield, %	HCl, m.p.	Base, m.p.
1-methyl-1H-imidazo(4,5-c)-quinoline	90	294-296 C	246-248 C
1-ethyl-1H-imidazo(4,5-c)-quinoline	83	273 C	64-66 C
1-[(3-dimethyl-amino)-propyl]-1H-imidazo(4,5-c)-quinoline		246-247 C	52-54 C
1-[(2-diethyl-amino)-ethyl]-1H-imidazo (4,5-c)-quinoline	90	252-254 C	48-50 C
1-iso-propyl-1H-imidazo(4,5-c)-quinoline	85	234-236 C	57-59 C
1-benzyl-1H-imidazo(4,5-c)-quinoline	75	252-254 C	174-176 C

	Yield, %	HCl, m.p.	Base, m.p.
1-(2-hydroxy-ethyl)-1H-imidazo(4,5-c)-quinoline ethane sulfonate	85	201-202 C	172-173 C
1-(2-phenyl-ethyl)-1H-imidazo (4,5-c)-quinoline	90	134-36 C H_2O	96-98 C
1-[2-(4-chlor-phenyl)-ethyl]-1H-imidazo (4,5-c)-quinoline	90	252-54 C	--
1,2-diethyl-1H-imidazo(4,5-c)-quinoline	86	253-256 C	149-151 C
1-ethyl-2-phenyl-1H-imidazo(4,5-c)-quinoline	89	--	
2-ethyl-1H-imidazo(4,5-c)-quinoline	85	256-258 C	206-208 C
2-phenyl-1H-imidazo(4,5-c)-quinoline	89	318-20 C	296-298 C
1-[(2-diethyl-amino)-ethyl]-2-phenyl-1H-imidazo(4,5-c)-quinoline	100	235-37 C	96-98 C
2-ethyl-1-(2-hydroxy-ethyl)-1H-imidazo (4,5-c)-quinoline ethane sulfonate		146-148 C	216-218 C

Example 2

Preparation of 1H-imidazo(4,5-c)quinoline

We boil 2.0 g (0.0125 mole) of 3,4-diamino-quinoline with 50 ml of 100% formic acid for 12 hours, then evaporate the resulting solution until dry. We dissolve the obtained mass of crystals in 50 mg of water, and adjust the reaction to pH = 7 with sodium hydrogen carbonate. We dry the precipitating white crystals and wash with water. Weight: 2.0 g. Yield: 94.8%, melting point: 284 degrees C.

Example 3

Preparation of 2-(2-methoxy-phenyl)-1H-imadazo(4,5-c)quinoline.HCl

We mix 23.2 g (0.1 mole) of 3,4-diamino-quinoline hydrochloride and 15.2 g (0.1 mole) of 2-methoxy-benzoic acid with 230 ml of phosphorus oxychloride. We heat the temperature of the mixture to boiling and boil for 8 to 10 hours. After this, we distill off the excess phosphorus oxychloride at reduced pressure and pour the remainder onto 2000

g of ice during intense mixing. We dry the precipitating crystals and wash with acetone. Weight: 23.5 g. Yield: 85.5%. Melting point: 268-270 degrees C.
In similar manner we prepare the following compounds:
1-[(2-diethyl-amino)-ethyl]-2-methoxy-phenyl-1H-imidazo(4,5-c)quinoline
m.p.: 99 to 101 degrees C, HCl salt 192 to 194 degrees C
1-diethyl-amino-ethyl-2--phenyl-1H-imidazo(4,5-c)quinoline
1-(diethyl-amino-ethyl)-2-(3,4-dimethoxy-benzyl)-1H-imidazo(4,5-c)quinoline, yield 75%, HCl salt
m.p.: 220-22 degrees C, base m.p.: 135-35 degrees C.

Example 4

Preparation of 2-phenyl-1H-imidazo(4,5-c)quinoline

We boil 23.2 g (0.1 mole) of 3,4-diamino-quinoline hydrochloride and 21.0 g (0.1 mole) of benzaldehyde sodium hydrogen sulfite in 200 ml of ethyl alcohol for 4 to 5 hours with reflux cooling. After cooldown, we dry the obtained crystal mass and remove the inorganic salts by washing several times with cold water. After drying the white, porous Schiff base, we react it in 200 ml of nitrobenzene for 4 hours at 190 degrees C. After cooling and mixing with 350 ml of water, a grayish white crystal mass precipitates from the mixture. We dry this and wash with ethanol. Weight of the thus obtained 2-phenyl-1H-imidazo(4,5-c)quinoline: 16.0 g. Yield: 65%. Melting point: 296 to 298 degrees C.

Example 5

Preparation of 2-ethyl-1H-imidazo(4,5-c)quinoline

We mix 15.9 g (0.1 mole) of 3,4-diamino-quinoline with 95 g of propionic acid anhydride, then boil under reflux cooling for 2 hours. After cooling, we slowly pour the reaction mixture into 600 ml of water and adjust the pH to 7 with 40% sodium hydroxide solution. The base precipitates in the form of a white, flaky precipitate. Weight: 15.76 g. Yield: 80%. Melting point: 206 to 208 degrees C.

Example 6

Preparation of 2-phenyl-1H-imidazo(4,5-c)quinoline

We mix 23.2 g (0.1 mole) of 3,4-diamino-quinoline hydrochloride with 100 g of benzoic acid anhydride and slowly raise the temperature to 170 degrees C. We obtain a melt, which we hold at the given temperature for two hours, then mix with 200 ml of xylene and boil for 30 minutes. After cooling, we dry the obtained crystal mass, wash with ethanol, then suspend in 1000 ml of water. We adjust the reaction to pH = 7 with sodium hydrogen carbonate. The weight of the thus obtained 2-phenyl-1H-imidazo(4,5-c) quinoline: 18.6 g. Yield: 76%, melting point: 296 to 298 degrees C.

Example 7

4-diacetamino-3-nitro-quinoline

We boil 18.9 (0.1 mole) of 4-amino-3-nitro-quinoline with 100 ml of acetic acid anhydride in the presence of 0.1 g anhydrous sodium acetate for 2 hours under reflux cooling. After expiration of the reaction time, we obtain the target compound by treating the resulting solution with water, and its weight is 25.5 g. Yield: 93.4%, melting point: 118 to 120 degrees C. The product in every case is contaminated with a little bit of the monoacetyl derivative.

Example 8

Preparation of 4-acetamino-3-nitro-quinoline

We suspend 2.7 g (0.01 mole) of 4-diacetamino-3-nitro-quinoline in 100 ml of water and adjust the reaction to pH = 9 with 0.5 ml of 40% sodium hydroxide solution. We mix the suspension for 1.5 hours at 60 degrees C, then cool, adjust the pH to 6 with hydrochloric acid, and dry the white crystals and wash with water. Weight: 2.3 g. Yield: 100%, melting point: 225 to 227 degrees C.

Example 9

Preparation of 4-acetamino-3-amino-quinoline

We hydrogenate 11.55 g (0.05 mole) of 4-acetamino-3-nitro-quinoline in 200 ml of ethanol in the presence of 5% charcoal palladium catalyst at room temperature and atmospheric pressure. After removing the catalyst, we obtain the target compound by evaporation of the resulting solution in an inert atmosphere. Weight: 8.55 g. Yield: 85%, melting point: 209 to 210 degrees C.

Example 10

Preparation of 2-methyl-1H-imidazo(4,5-c)quinoline.HCl

We melt 4.0 g (0.02 mole) of 4-acetamino-3-amino-quinoline in 200 ml of ethanol by heating it, then boil under reflux cooling for 1 hour with 15 ml of ethanol containing 20% hydrochloric acid. After cooling, we dry the resulting snow-white crystals and wash with ethyl acetate. The hydrochloride salt obtained in this way corresponds in every respect with the 2-methyl-1H-imidazo(4,5-c)quinoline obtained by other methods.

Example 11

Preparation of 1-caproyl-amino-2-methyl-imidazo(4,5-c)quinoline

We mix 16.5 g (0.05 mole) of 1-acetyl-3-amyl-1,2-dihydro-as-triazino(4,5-c)quinoline hydrochloride with 140 ml of 5% hydrochloric acid for one hour at 80 degrees C. During

this process, the dark red color of the crystals brightens. After cooling, the weight of the dried crystals is: 15.0 g. Yield: 91%, melting point: 273 to 275 degrees C.
By suspending the obtained hydrochloride salt in water, and adjusting the reaction to 8 with sodium hydrogen carbonate, we obtain 13.0 g of 1-caproyl-amino-2-methyl-imidazo(4,5-c)quinoline, whose melting point is 126 to 128 degrees C, and contains 1 mole of water of crystallization.
In similar manner we prepare the following compounds:

]

	yield, %	HCl m.p.	base m.p.
1-(pentanoyl-amino)-2-methyl-imidazo-(4,5-c)quinoline	83	256-258 C	130-132 C
1-(nonanoyl-amino)-2-methyl-imidazo-(4,5-c)quinoline	97	236-238 C	117-118 C
1-(acetyl-amino)-2-methyl-imidazo(4,5-c) quinoline	74	276-278 C	156-157 C
1-(benzoyl-amino)-2-methyl-imidazo(4,5-c) quinoline	88	260-262 C	165-165 C
1-(pivaloyl-amino)-2-methyl-imidazo(4,5-c) quinoline	70	262-265 C	164-166 C
1-(acetyl-amino)-imidazo(4,5-c)quinoline	82	305-307 C	131-132 C
1-(propionyl-amino)-imidazo(4,5-c) quinoline	81	293-294 C	235-236 C

Example 12

Preparation of 1-amino-2-methyl-imidazo(4,5-c)quinoline

We boil 6.65 g (0.025 mole) of 1-caproyl-amino-2-methyl-imidazo(4,5-c)quinoline hydrochloride with 60 ml of concentrated hydrochloric acid for 5 hours. After cooling, we dry the precipitated crystals and wash with ethyl acetate. The weight of the obtained snow-white crystals is 4.6 g. Yield: 84%, melting point: 350 to 352 degrees C.
By suspending the obtained hydrochloride salt in water, and adjusting the pH to 8 with sodium hydrogen carbonate, we obtain the 1-amino-2-methyl-imidazo(4,5-c)quinoline base, whose melting point is 214 to 216 degrees C.
The melting point of the 1-amino-imidazo(4,5-c)quinoline hydrochloride, prepared in similar manner, is 282 to 283 degrees C, that of the base is 224 to 226 degrees C.
In similar manner we further prepare the following compounds:

1-amino-2-butyl-imidazo(4,5-c)quinoline.HCl	282-283 degrees C
1-amino-2-butyl-imidazo(4,5-c)quinoline	m.p. 148-150 degrees C

Example 13

Preparation of 2-methyl-1H-imidazo(4,5-c)quinoline

We dissolve 1.98 g (0.01 mole) of 1-amino-2-methyl-1H-imidazo(4,5-c)quinoline in a mixture of 15 ml of water and 15 ml of concentrated hydrochloric acid. Holding the temperature between 0 and –5 degrees C, we add by drops 1 g (0.015 mole) of a concentrated aqueous solution of sodium nitrite and agitate the reaction mixture at this temperature for two hours. After the reaction time has expired, we let cool down to room temperature and adjust the pH to 7 with a 40% sodium hydroxide solution, dry the precipitated crystals, suspend in 20 ml of water, and liberate the base by adding a little sodium hydrogen carbonate. The weight of the resulting white crystals is 1.0 g. Yield: 55%, melting point 246 to 248 degrees C. The melting point of the hydrochloride separated with ethanol hydrochloride from the ethanol solution of the base is 294 to 296 degrees C.
By a similar method we prepare 1H-imidazo(4,5-c)quinoline with 1-amino-imidazo(4,5-c)quinoline diazotation. The melting point is 282 to 284 degrees C, the hydrochloride salt melts at 314 to 316 degrees C.

Example 14

Preparation of 7,8-dimethoxy-1H-imidazo(4,5-c)quinoline

The preparation occurs in the way described for example 1. Yield: 85%, HCl salt m.p.: 290-92 degrees C, m.p. of the base: 257-59 degrees C.

Example 15

Preparation of 1-[2-(4-methoxy-phenyl)-ethyl]-1H-imidazo(4,5-c)quinoline

The preparation occurs in the way described for example 1. Yield: 90%, ethane sulfonic acid salt m.p.: 190-92 degrees C.

Preparation of 2-benzyl-1-[(2-diethyl-amino)-ethyl]-1H-imidazo(4,5-c)quinoline

The preparation occurs in the way described for example 3. Yield: 70%, HCl salt m.p.: 240-42 degrees C, m.p. of the base: 87-88 degrees C.

Example 16

Preparation of 1-[(2-diethyl-amino)-ethyl]-2-phenyl-1H-imidazo(4,5-c)quinoline

The preparation occurs in the way described for example 3. Hydrochloride salt m.p.: 235-37 degrees C, m.p. of the base: 96-98 degrees C.

Patent claims

1. Method for preparation of the new imidazo(4,5-c)quinolines of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon straight or

branched chain alkyl group possibly substituted with a hydroxyl group, or a phenyl group possibly substituted by a 1-4 carbon alkoxy group or a phenyl-(1-4 carbon) alkyl group possibly substituted by a 1-4 carbon alkoxy group or one or more halogen atoms in the benzene ring or a di(1-4 carbon) alkylamino-(1-4 carbon) alkyl group, amino group, -NH-CO-R group (where the meaning of R is a 1-10 carbon straight or branched chain alkyl group, a phenyl-1-4 carbon alkyl group or a phenyl group), the meaning of R2 is a hydrogen atom, a 1-4 carbon straight or branched chain alkyl group, or a phenyl group possibly substituted with a 1-4 carbon alkoxy group, or a phenyl-1-4 carbon-alkyl group, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon alkoxy group, and their pharmacologically acceptable salts, characterized in that

a) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon atom straight or branched chain alkyl group possibly substituted with a 1-4 carbon atom alkoxy group, a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group, a phenyl-(1-4 carbon atom) alkyl group possibly substituted by a 1-4 carbon atom alkoxy group or one or more halogen atom in the benzene ring or a di(1-4 carbon atom) alkylamino-(1-4 carbon atom) alkyl group, the meaning of R2 is as given, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon atom alkoxy group, we react any compound of general formula (II), where R1, R7 and R8 in the formula have the above meaning, with an orthoester of general formula (III), where the meaning of R2 in the formula is as given above, the meaning of Alk is a 1-4 carbon alkyl group, or with a carboxylic acid of general formula (IV), where the meaning of R2 in the formula is as given above, or with an aldehyde of general formula (V), where the meaning of R2 in the formula is as given above, or

b) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, a 1-4 carbon straight or branched chain alkyl group possibly substituted with a 1-4 carbon alkoxy group, a phenyl group possibly substituted by a 1-4 carbon atom alkoxy group, a phenyl-(1-4 carbon) alkyl group possibly substituted by a 1-4 carbon alkoxy group or one or more halogen atoms in the benzene ring or a di(1-4 carbon) alkylamino-(1-4 carbon) alkyl group, the meaning of R2 is as given, but other than hydrogen atom, the meaning of R7 and R8 is a hydrogen atom or a 1-4 carbon alkoxy group, we react any compound of general formula (II), where R1, R7 and R8 in the formula have the above meaning, with an anhydride of general formula (IX), where the meaning of R2 in the formula is as given above, or

c) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1, R2, R7 and R8 in the formula is as above, we acylate any compound of general formula (VIII), where the meaning of R1, R7 and R8 in the formula is as above, with an anhydride of general formula (IX), where the meaning of R2 in the formula is as given above, or with an acid halide of general formula (X), where the meaning of R2 in the formula is as given above and the meaning of X is a halogen atom, we reduce the resulting compound of general formula (VI), where the meaning of R1, R2, R7 and R8 in the formula is as above, and we treat the resulting compound of general formula (VII), where the meaning of R1, R2, R7 and R8 in the formula is as above, with an acid catalyst in a polar solvent, preferably alcohol, dimethyl

formamide, or dimethyl sulfoxide, or a mixture of these, at temperature of 0 to 200 degrees C, or

d) for the preparation of such imidazo(4,5-c)quinolines as belong to the compounds of general formula (I), where the meaning of R1 in the formula is a hydrogen atom, amino group, -NH-CO-R group (where the meaning of R is a 1-10 carbon straight or branched chain alkyl group, a phenyl-1-4 carbon alkyl group or a phenyl group), the meaning of R2, R7 and R8 is as above, we treat any compound of general formula (XI), where the meaning of R and R2 in the formula is as above, with acid and if desired we boil the obtained compound of general formula (Ia), where the meaning of R and R2 in the formula is as above, with concentrated acid, and if so desired we react the obtained compound of general formula (Ib), where the meaning of R2 in the formula is as given above, with acidic sodium nitrite, or

e) for the preparation of compounds of general formula (Ia), belonging to the group of compounds with general formula (I), where the meaning of R in the formula is as given above, we acylate any compound of general formula (Ib), where the meaning of R2 in the formula is as given above, with a compound containing a group of general formula R-CO-, where the meaning of R in the formula is as given above, and if so desired we transform the resulting compounds of general formula (I) into pharmaceutically acceptable acid addition salts, or liberate the base from the salt.

2. Method for the preparation of a pharmaceutical product of primarily tranquilizing and/or antidepressant, antispasmodic, analgesic, antiperistaltic, and antisecretory action containing any of the compounds of general formula (I), where the meaning of R1, R2, R7, R8 in the formula is as given in claim 1, characterized in that we mix any compound of general formula (I), obtained according to claim 1, where the meaning of R1, R2, R7, R8 in the formula is as given above, or their pharmaceutically acceptable salt, with the customary bases used in pharmacology, and transform them into the pharmaceutical product.

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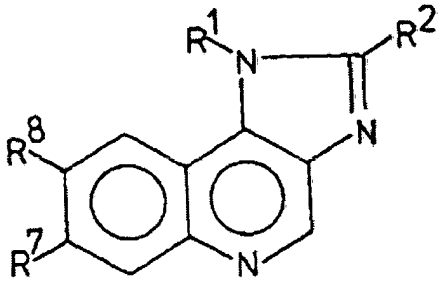

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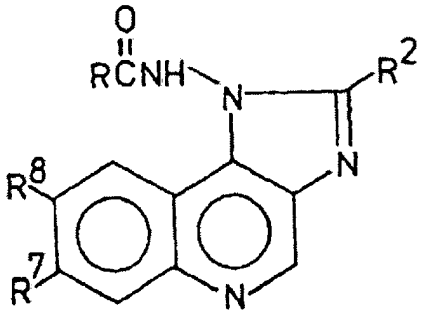

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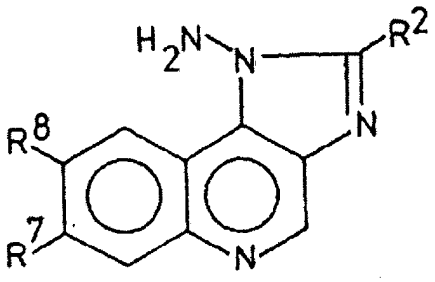

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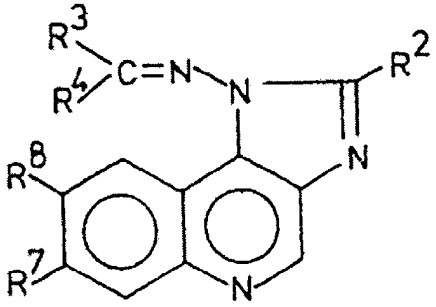

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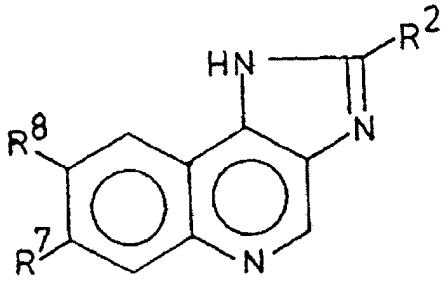

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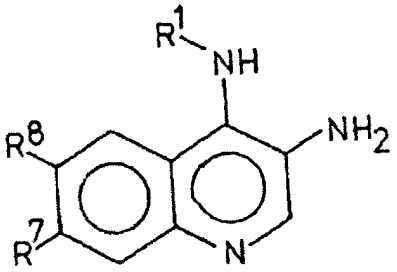

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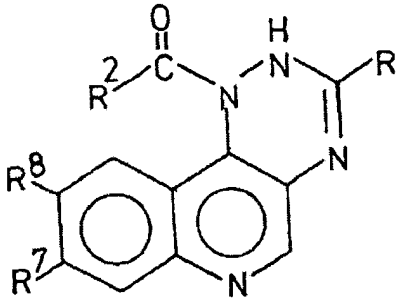
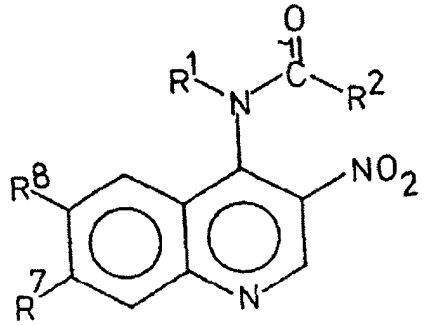


XI

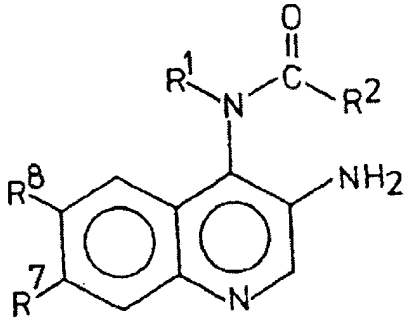
$R^2C(OAlk)_3$ III

R^2COOH IV

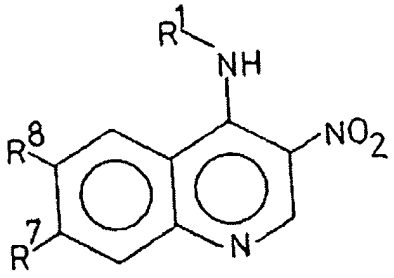
R^2CHO V



VI



VII



VIII

$(R^2CO)_2O$ IX

R^2COX X

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Cím: **Új eljárás 1H-imidazo-[4,5-c]-kinolin-származékok előállítására**

Angol cím: NEW PROCESS FOR THE PRODUCTION OF 1H-IMIDAZO(4,5-C)QUINOLIN DERIVATIVES

Jogosult: Riker Laboratories Inc., Saint Paul, Minnesota (US)
Feltaláló: Lagain, Daniel Jean-Marie, Malakoff (FR)
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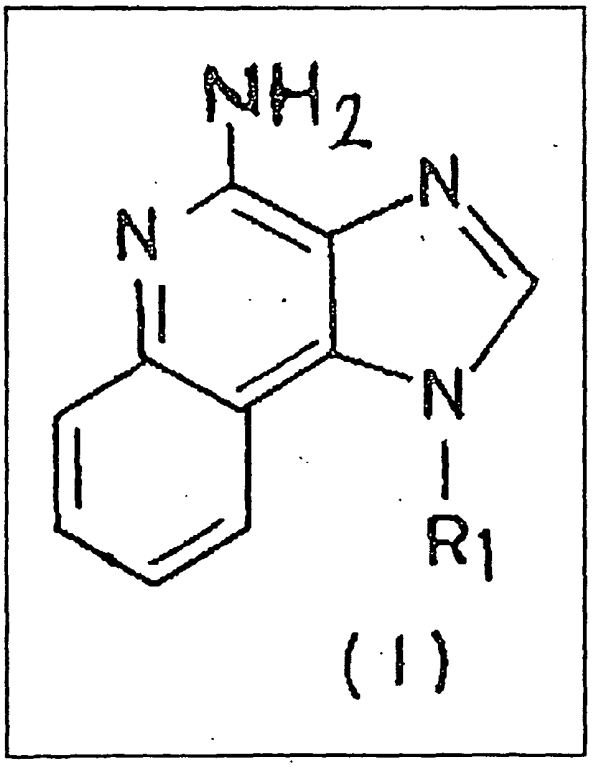

(I)

Kivonat (közzétételi):

A találmány szerinti új eljárás az (I) általános képletű vegyületek - a képletben

R_1 jelentése adott esetben rövidszénláncú alkil-, 3-6 szénatomos cikloalkil- vagy (rövidszénláncú) alkil-(3-6 szén-

atomos)cikloalkilcsoporttal szubsztituált 1-10 szénatomos alkil- vagy 3-10 szénatomos alkenilcsoport, vagy 1-6 szénatomos mono- vagy dihidroxi-alkil-csoport,

R_2 jelentése hidrogénatom, 1-8 szénatomos alkilcsoport vagy adott esetben rövidszénláncú alkil-, alkoxicsoporttal vagy halogénatommal a benzolgyűrűben mono- vagy diszubsztituált benzil-, fenetil-

vagy fenilcsoport,

R_4 jelentése adott esetben rövidszénláncú alkilcsoporttal mono- vagy diszubsztituált aminocsoport, rövidszénláncú alkil- vagy alkil-tio-csoport, fenil-tio- vagy morfolinocsoport,

R jelentése rövidszénláncú alkil-, alkoxicsoport vagy halogénatom, és

n értéke 0-2 - előállítására vonatkozik oly módon, hogy egy (IV) általános képletű vegyületet egy (VIII) általános képletű aminnal reagáltatnak,

a kapott (V) általános képletű vegyületet redukálják, a kapott (VI) általános képletű vegyületet egy (IX) vagz (X) általános képletű vegyülettel, vagy azok elegyével reagáltatják, a kapott (VII) általános képletű vegyületet egy (XI) vagy (XII) általános képletű vegyülettel reagáltatják, a képletekben

R, R_1, R_2, R_4 és n jelentése a fenti,

Alkil jelentése 1-8 szénatomos alkilcsoport és

M jelentése alkálifématom.

Az (I) általános képletű vegyületek hörgőtágító vagy antivirális hatásuk következtében gyógyszerkészítmények hatóanyagaként használhatók.

Igénypont:

Eljárás az (I) általános képletű vegyületek - a képletben
R1 jelentése egyenes vagy elágazó szénláncú 1-10 szénatomos alkilcsoport - előállítására, azzal jellemezve, hogy
(a1) egy (IV) képletű vegyületet egy (VIII) általános képletű aminnal - a képletben
R1 jelentése a tárgyi körben megadott -
reagáltatunk,
a kapott (V) általános képletű vegyületet - a képletben R1 jelentése a tárgyi körben megadott -
redukáljuk,
a kapott (VI) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott -
hangyasavval vagy annak (IX) általános képletű ortoészterével - a képletben
Alkil jelentése egymástól függetlenül egyenes vagy elágazó szénláncú 1-8 szénatomos alkilcsoport -
reagáltatjuk, és
a kapott (VII) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott - ismert módon ammóniával vagy egy (XII) általános képletű alkálifémamiddal - a képletben
M jelentése alkálifématom -
reagáltatjuk inert oldószerben,
vagy
(a2) egy (V) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott -
redukálunk,
a kapott (VI) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott -
hangyasavval vagy annak (IX) általános képletű ortoészterével - a képletben
Alkil jelentése egymástól függetlenül egyenes vagy elágazó szénláncú 1-8 szénatomos alkilcsoport -
reagáltatjuk, és
a kapott (VII) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott - ismert módon ammóniával vagy egy (XII) általános képletű alkálifém-amiddal - a képletben
M jelentése alkálifématom -
reagáltatjuk inert oldószerben,
vagy
(a3) egy (VI) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott -

hangyasavval vagy annak (IX) általános képletű ortoészterével - a képletben
Alkil jelentése egymástól függetlenül egyenes vagy elágazó szénláncú 1-8 szénatomos alkilcsoport - reagáltatjuk, és a kapott (VII) általános képletű vegyületet - a képletben
R1 jelentése a tárgyi körben megadott - ismert módon ammóniával vagy egy (XII) általános képletű alkálifémamiddal - a képletben
M jelentése alkálifématom -
reagáltatjuk inert oldószerben.

Intézkedések

0. Szabadalmi bejelentés közzététele (CV)
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6. Szabadalom megadása (BZ)
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